Remarks

I. Support for the Amendment

Support for the amendment to claim 8 can be found in the specification, for example, at page 3, line 25.

Support for new claim 56 can be found in the specification, for example, at page 20, lines 3-7.

Support for new claims 57-62 can be found in the specification, for example, at page 20, lines 18-25; at page 14, lines 1-5; at page 19, lines 16-21; at page 18, lines 5-21; and at page 22, lines 12-18.

Support for new claims 63-69 can be found in the specification, for example, at page 27, lines 17-19; at page 9, line 20 through page 10, line 8; at page 14, lines 1-5; at page 19, lines 16-21; at page 18, lines 5-21; and at page 22, lines 12-18.

II. Status of the Claims

By the foregoing amendments, claims 38-55 are sought to be cancelled without prejudice or disclaimer. Applicants reserve the right to prosecute the subject matter of the cancelled claims in other applications. Claim 8 has been amended, and claims 56-69 are sought to be added.

Upon entry of the foregoing amendments, claims 8-13 and 56-69 are pending in the application, with claims 8, 57, and 63 being the independent claims. Based on the above

amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

III. Rejections under 35 U.S.C. § 112, second paragraph

In the Office Action, at page 2, lines 13-15, the Examiner rejected claims 8-13, and 50-55 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the inventive subject matter. Applicants respectfully traverse the rejection.

According to the Examiner, "Claim 8 (9-13 dependent on) is indefinite in that it is unclear and vague in the recitation 'a crude preparation containing DNA' because it is unclear what is to be encompassed by 'a crude preparation containing DNA'." Applicants respectfully disagree.

The term "crude preparation" is described in the specification as a preparation that contains some nucleic acids that have been released from the cells without the need for purification of the nucleic acid from the cells. As stated in the specification:

> Preparation of crude extracts of cells or tissues may be accomplished by standard procedures which allows removal of at least some nucleic acids from the cell or tissue *without the need for purification of the nucleic acids from the cells, tissue or cell/tissue debri, although nucleic acids may be isolated or purified or partially purified* prior to the use in accordance with the invention.

Specification, page 20, lines 7-12. (Emphasis added). Applicants respectfully request that the objection to the phrase "crude preparation" be withdrawn. If the Examiner maintains the rejection, he is respectfully requested to explain why the recitation of a "crude preparation" is indefinite.

In an effort to expedite prosecution, Applicants have canceled claims 50-55, and thus, the Examiner's rejection of these claims is moot, and the rejection of the remaining claims should be withdrawn.

IV. Rejections under 35 U.S.C. § 112, first paragraph

In the Office Action, at page 3, lines 11-15, the Examiner rejected claims 38-43, 44-49, and 50-55 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection. However, in an effort to expedite prosecution, Applicants have cancelled claims 38-43, 44-49 and 50-55 without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to prosecute the subject matter of the cancelled claims in other applications.

V. Rejections under 35 U.S.C. § 102

A. Claims 8-12, 38-43, and 50-55 are rejected as being anticipated by Maudru et al.

At page 4 of the Office Action, the Examiner has maintained the rejection of claims 8-12 and rejected claims 38-43, and 50-55 under 35 U.S.C. § 102(a) as being anticipated by Maudru *et al.*, *Journal of Virological Methods 66:* 247-261, 1997 (hereinafter "Maudru"). Applicants respectfully traverse the rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

The Examiner stated:

> It is acknowledged that Maudru et al. teach a method that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. It is at this point where Maudru et al. anticipates the claimed methods in that the starting material is now a DNA containing preparation and in as much as no additional purification steps have been done to this preparation, it could be considered a "crude DNA-containing preparation".

Office Action, page 4, line 18 through page 5, line 1. Applicants respectfully disagree.

Amended claim 8 (claims 9-13 that depend therefrom) is drawn to a method for the synthesis of nucleic acid molecules, wherein a "crude preparation" containing DNA, which functions as the desired nucleic acid template, is mixed with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity. Maudru relates to a method, wherein the first step comprises mixing "pure" RNA with a polypeptide with reverse transcriptase activity. Maudru fails to teach a method for nucleic acid synthesis that begins with mixing a "crude preparation." Maudru states:

> Brome mosaic virus (BMV) RNA was purchased from Promega (Madison, WI; catalogue number D1541), while MS2 and tobacco mosaic virus (TMV) were from Boehringer-Mannheim (Indianapolis, IN; catalogue numbers 165948 and 1120387, respectively).

Maudru, page 249, first full paragraph.

The descriptions provided for the MS2 RNA and the TMV RNA in Boehringer Mannheim's catalog describe the RNA as being "free of host nucleic acid and protein" (See Exhibit A). Clearly, this is distinct from a "crude preparation."

The Examiner argues that "[t]he starting material is now a DNA containing preparation and in as such no additional purification steps have been done to this preparation, it could be considered a "crude DNA-containing preparation". Office Action, at page 4, line 18 through page 5, line 2. Applicants respectfully disagree with this assertion.

Maudru synthesizes a complementary DNA strand from a purified RNA molecule, however, one of ordinary skill in the art is unlikely to refer to a preparation containing purified RNA and its cDNA as a "crude preparation."

Therefore, Maudru fails to anticipate the claimed invention because it fails to teach a method for nucleic acid synthesis that begins with a "crude preparation" containing DNA. The rejection of claims 8-13 should be withdrawn.

In an effort to expedite prosecution, Applicants have canceled claims 38-55 without prejudice or disclaimer, and thus, this aspect of the Examiner's rejection has been rendered moot.

These claims have been replaced with a new set of claims directed to use of either genomic DNA or a vector as starting material. None of these claims are anticipated by Maudru.

B. Claims 8-12 are rejected as being anticipated by Don et al.

At page 6 of the Office Action, the Examiner rejected claims 8-12, and 50-55 under 35 U.S.C. § 102(b) as being anticipated by Don *et al.*, *Nucleic Acid Research* 21(3):783, 1993 (hereinafter Don). Applicants respectfully traverse this rejection. In any event, the rejection is moot as it concerns claims 50-55.

As discussed *supra*, amended claim 8 recites a method for nucleic acid synthesis from a crude preparation containing DNA that functions as the nucleic acid template. In this way, the claimed method is quite distinct from the method disclosed by Don.

Don refers to a method for the synthesis of nucleic acid molecules wherein the first step comprises mixing ***pure*** RNA with a reverse transcriptase. Don fails to teach the synthesis of nucleic acid molecules from a crude preparation containing DNA. Don states:

> Total RNA was prepared by a scaled down acid-phenol extraction as described by Chomczynski *et al.* [citation omitted]. Cells were added to 100 ul of solution D and all other reagents were scaled down proportionately.

Don, page 783, 2nd paragraph.

The Examiner stated, "[F]urther to this point, Don et al. actually begin their taught methods with 'Cells' which are added to 100 ul of solution D [citation omitted] (Office Action, page 7, lines 6-9). This surely would be encompassed by a 'crude-preparation containing'." Applicants respectfully disagree that this recitation results in Don anticipating the claimed invention.

Regardless of the material Don begins with, Don still fails to mix a crude preparation containing DNA, wherein DNA functions as a desired nucleic acid template, with one of more DNA polymerases, and one or more peptides or polypeptides having ribonuclease

activity. Applicants respectfully point out that the cells were added to solution D for the purpose of isolation and purification of the RNA. Therefore, Don begins his method with a purified RNA template. Nowhere, however, does Don teach mixing a crude preparation containing DNA with peptides or polypeptides having ribonuclease activity and a DNA polymerase.

The Examiner states:

> It is acknowledged that Don et al. teach a method that begins with a RNA-containing preparation, but this is converted to a DNA-containing preparation during the reverse transcriptase step. It is at this point where Don et al. anticipates the claimed methods in the starting material is now a DNA containing preparation and in as much no additional purification steps have been done to this preparation, it could be considered a "crude DNA-containing preparation".

Office Action, at page 6, line 22 through page 7, line 5. Applicants respectfully disagree with this assertion.

One of ordinary skill in the art is unlikely to refer to a preparation containing purified RNA and its cDNA as a "crude preparation." Clearly, this fails to meet the description of a "crude preparation" as set forth earlier in this reply.

Don fails to anticipate the claimed invention because Don fails to teach mixing a crude preparation that contains DNA with peptides or polypeptides having ribonuclease activity, and a DNA polymerase. In fact, Don teaches away from the invention of claim 8 because Don teaches that the nucleic acid template should be isolated and purified. Thus, Don fails to anticipate the claimed method. Applicants respectfully request that this rejection be withdrawn.

In an effort to expedite prosecution, Applicants have canceled claims 50-55, and thus, the Examiner's rejection has been rendered moot.

A new set of claims has been added that are directed to the use of either genomic DNA or a vector as starting material. None of these claims are anticipated by Don.

VI. Rejection under 35 U.S.C. § 103

The Examiner rejected claims 8-13, and 38-55 under 35 U.S.C. § 103(a) as being unpatentable over Maudru *et al.* (*Journal of Virological Methods 66:* 247-261, July 1997) or Don *et al.* (*Nucleic Acids Research 21(3):* 783, 1993). Applicants respectfully disagree.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, this burden has not been satisfied.

A. Rejections in View of Maudru

The Examiner rejected claims 8-13 under 35 U.S.C. § 103(a) as being unpatentable over Maudru *et al.* In making this rejection, the Examiner contends:

> With respect to Maudru et al. this motivation [to use both a DNA polymerase and a RNase together] is suggested in the abstract in which Maudru et al. states that the background signal of the PBRT assay was found to be due to an intrinsic RNA-dependent DNA polymerase activity of the Taq DNA polymerase. Thus their exists motivation for the use of a ribonuclease together with Taq DNA polymerase in any

> method in which Taq DNA polymerase will be used to synthesize a nucleic acid.

Office action, page 8, lines 17-22. Applicants respectfully disagree with these contentions.

As discussed *supra*, the method of Maudru does not teach a method for nucleic acid synthesis that begins with a crude preparation containing DNA. Nor does Maudru suggest such a method. Rather, the method of Maudru uses purified RNA as the starting nucleic acid template.

One of ordinary skill in the art would not have been motivated to modify the teachings of Maudru to obtain the invention of claim 8 (and those claims dependent therefrom) because Maudru stresses the importance of purified RNA. According to Maudru:

> To avoid some of the sources of potential contamination, templates for two of the methods were chosen to be from the genome of RNA viruses that had no DNA in their life cycles and whose sequences had little homology with mammalian genomes. . . .

Maudru, page 248, column 2, lines 4-8.

At page 9 of the Office Action, the Examiner further stated "one of ordinary skill in the art would have been motivated to use the method of claim 10 to synthesize a nucleic acid molecule wherein one or more of said nucleotides are detectably labeled so that the synthesized DNA molecule could be used as a probe to isolate similar DNA molecules from a DNA library, or so that the label could be used as a means of measuring the amount of DNA synthesized." Applicants respectfully point out that claim 13, and not claim 10, relates to the use of detectably labeled nucleotides, and traverse the rejection as it applies to claim 13.

Claim 13, which relates to the use of detectably labeled nucleotides, depends from claim 8. Because Maudru fails to suggest a method for nucleic acid synthesis that begins by

mixing a crude preparation containing DNA (*i.e.*, the method of claim 8), it also fails to suggest the invention of claim 13, which has the additional limitation of detectably labeled nucleotides. Clearly, one of ordinary skill in the art would not have been motivated to modify the teachings of Maudru to obtain the claimed invention because Maudru stresses the importance of purified RNA. Therefore, Maudru fails to render obvious the invention of claim 8, and the claims dependent therefrom.

In an effort to expedite prosecution, Applicants have canceled claims 38-55 without prejudice or disclaimer, and therefore, the Examiner's rejection has been rendered moot.

These claims have been replaced with a new set of claims directed to use of either genomic DNA or a vector as starting material. None of these claims are rendered obvious by Maudru.

B. Rejections in View of Don

The Examiner rejected claims 8-13, and 38-55 under 35 U.S.C. § 103(a) as being unpatentable over Don *et al.* Applicants respectfully traverse this rejection.

As discussed *supra*, Don relates to a method of nucleic acid synthesis that uses purified RNA, and therefore, fails to anticipate the claimed invention. Don provides no motivation or suggestion for using crude preparations that contain DNA for the synthesis of nucleic acid molecules.

One of ordinary skill in the art would not have been motivated to mix a crude preparation containing DNA with a DNA polymerase and one or more peptides or polypeptides having ribonuclease activity because Don stresses the importance of purified RNA. The fact that Don teaches a four (4) hour RNA purification protocol (Chomczynski

et al., page 156, 2nd column) suggests that the purity of the RNA is an essential element of the disclosed method. Thus, Don is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness, and the rejection should be withdrawn.

At page 9 of the Office Action, the Examiner stated "one of ordinary skill in the art would have been motivated to use the method of claim 10 to synthesize a nucleic acid molecule wherein one or more of said nucleotides are detectably labeled so that the synthesized DNA molecule could be used as a probe to isolate similar DNA molecules from a DNA library, or so that the label could be used as a means of measuring the amount of DNA synthesized." Applicants respectfully point out that claim 13, and not claim 10, relates to the use of detectably labeled nucleotides. Applicants respectfully traverse the rejection as it applies to claim 13.

Claim 13, which relates to the use of detectably labeled nucleotides, depends from claim 8. Don fails to suggest mixing crude preparations containing DNA, wherein the DNA functions as a nucleic acid template, with one or more DNA polymerases, one or more peptides having ribonuclease activity, and detectably labeled nucleotides. Don makes no mention of detectably labeled nucleotides, and provides no motivation for the use of crude preparations containing DNA, which functions as the desired nucleic acid template. Therefore, Don is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness, and the rejection should be withdrawn.

In an effort to expedite prosecution, Applicants have canceled claims 38-55 without prejudice or disclaimer, and thus, the Examiner's rejection has been rendered moot.

These claims have been replaced with a new set of claims directed to use of either genomic DNA or a vector as starting material. None of these claims are rendered obvious by Don.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (202) 371-2589.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: October 19, 2001

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Version with markings to show changes made

Claims:

Amend the following claim:

8. (Twice amended) A method for synthesizing a nucleic acid molecule from a crude preparation containing DNA, said method comprising:

a) mixing the crude preparation containing DNA wherein the DNA functions as a desired nucleic acid template, with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and

b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said template.

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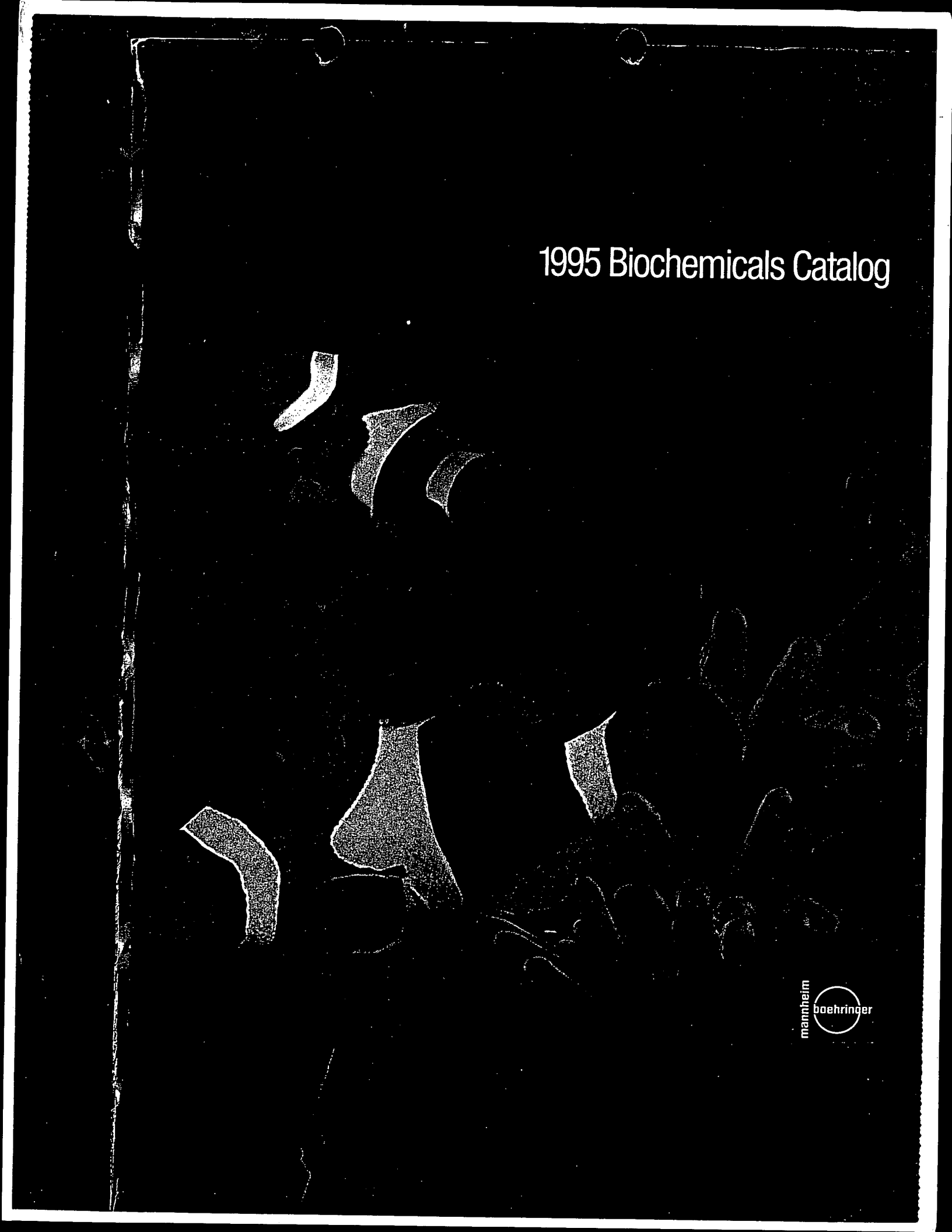

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General DNAs and RNAs continued

Product	Application	Characteristics	Cat. No.	Pack Size	Price
RNA from yeast	Studies as natural RNA in *in vivo* and *in vitro* protein-synthesizing system	**Form:** dry powder **Typical analysis:** RNA (absorbance) 95%, PI 0.3%	109 223	100 g	$ 41.00
RNA, MS2 from bacteriophage MS2	1. Studies as natural RNA in *in vivo* and *in vitro* protein-synthesizing system. (Initiation, elongation and termination of polypeptide synthesis). 2. Structural studies and functional studies	**Storage buffer:** 100 mM NaCl, 10 mM Tris-HCl, 1 mM $MgCl_2$, pH 7.5 **Molecular weight:** approx. 1200 kD **Size:** 3569 b **Typical analysis:** free from protein and host nucleic acids and contains < 10% of degradation products	165 948	10 A_{260} units (0.5 ml)	60.00
RNA, 5S-ribosomal from *E. coli* MRE600	1. Molecular weight standards in gel electrophoresis and ultra centrifugation. 2. Studying the structure and function of ribosomes	**Storage buffer:** 100 mM NaCl, 10 mM Tris-HCl, 1 mM $MgCl_2$, pH 7.5 **Size:** 120 b **Typical analysis:** free from 16S- and 23S-RNA as well as from tRNA	206 911	20 A_{260} units (1 ml)	164.00
RNA, 16S- and 23S-ribosomal from *E. coli* MRE600	1. Molecular weight standards in gel electrophoresis and ultracentrifugation. 2. Studying the structure and function of ribosomes	**Storage buffer:** 100 mM NaCl, 10 mM Tris-HCl, 1 mM $MgCl_2$, pH 7.5 **Size:** 1700 b and 3500 b **Typical analysis:** two homogenous bands in ultracentrifugation corresponding to 16S and 23S-RNA	206 938	100 A_{260} units (1 ml)	56.00
RNA, TMV from Tobacco Mosaic Virus	1. Molecular weight marker in assembly studies 2. Polycistronic mRNA for *in vitro* translation (control substrate of the Translation Kits, ➲ *see page 99*).	**Storage buffer:** 100 mM NaCl, 10 mM Tris-HCl, 1 mM $MgCl_2$, pH 7.5 **Molecular weight:** 2100 kD **Size:** 6350 b **Concentration:** 200 µg/ml **Typical analysis:** The preparation is free of host nucleic acids and protein. It contains < 10% degradation products	1 120 387	20 µg (0.1 ml)	88.00

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